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## DECLARE – TIMI 58

Multicenter Trial to Evaluate the Effect of Dapagliflozin  
on the Incidence of Cardiovascular Events

### **Discussant**

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Please specifically note RWI relevant to the management of diabetes  
Astra Zeneca, Boehringer Ingelheim, Janssen, Sanofi, Novo Nordisk and Merck

# Type 2 Diabetes Mellitus - Facts

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- High-risk for mortality
- CV mortality - number 1 cause of death
- Risk for “macrovascular” complications
  - MI, PVD, and Stroke
- Risk for “microvascular” complications
  - Retinopathy, Neuropathy, and Nephropathy
- Risk for heart failure
- Worse outcomes with these complication
- **PREVENTION and TREATMENT of these complications central to T2DM management**

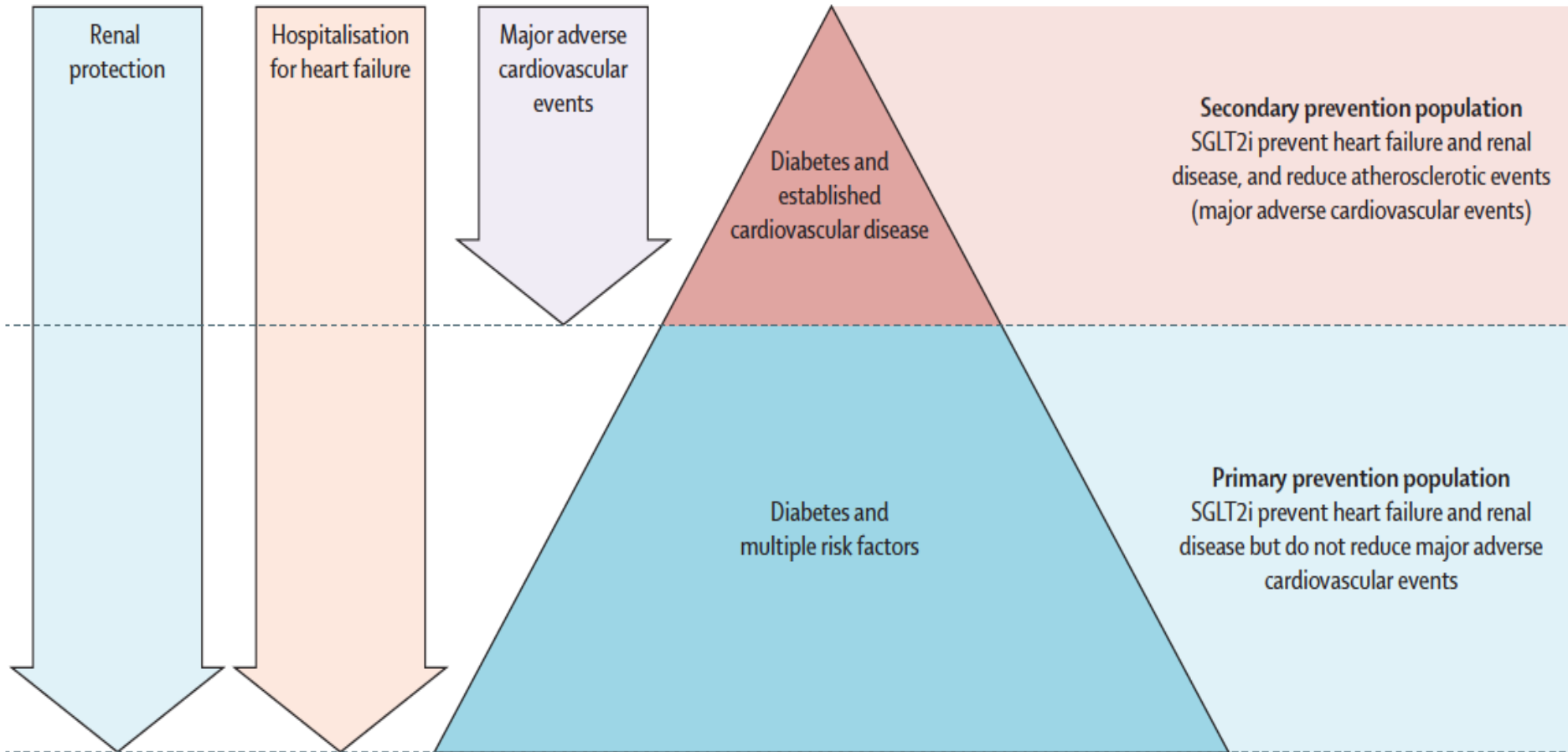
# DECLARE – TIMI 58

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- Well conducted trial
- Highest proportion of patients with risk factor but without established ASCVD among SGLT2i trials
- Confirms and replicate data from other studies with SGLT2i
  - Safety
  - HbA1c
  - Blood pressure
  - Weight

# SGLT2i and T2DM

## Cardiorenal efficacy of SGLT2i



**Pump, pipes, and filter: do SGLT2 inhibitors cover it all?**

Subodh Verma et al. *Lancet* 2018

# Interpretation

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- SGLT2i data cannot be taken in isolation from other T2DM trials and therapies
- All CV complications are all important
- Microvascular and macrovascular designation
  - Biologically overlapping
  - Not distinct concepts
- Macrovascular does not include heart failure
- CKD in T2DM should be studied independent of other “microvascular” diseases

# Heart Failure and T2DM

## Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D.,  
Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D.  
Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc.,  
Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D.,  
and Soffia Gudbjörnsdottir, M.D., Ph.D.

N ENGL J MED 379;7 NEJM.ORG AUGUST 16, 2018

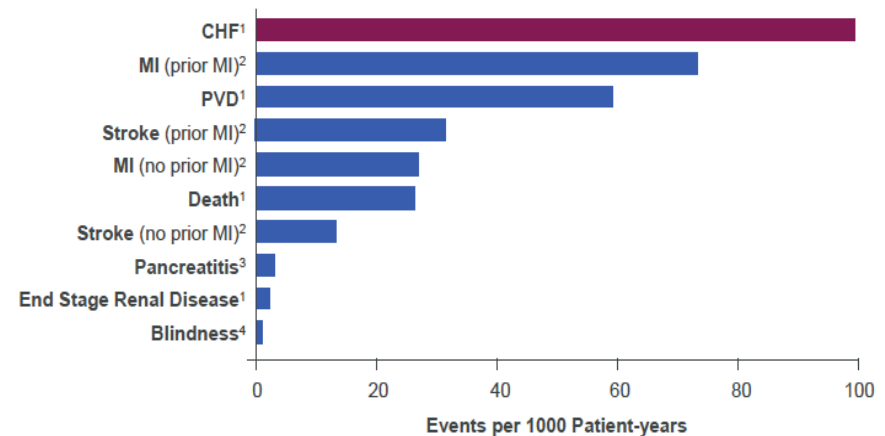
If 5 RF were controlled  
(H<sub>g</sub>A<sub>1c</sub>, smoking, LDLc, BP,  
albuminuria)

HR for AMI—0.84 (0.75-0.93)

HR for stroke—0.95 (0.84-1.07)

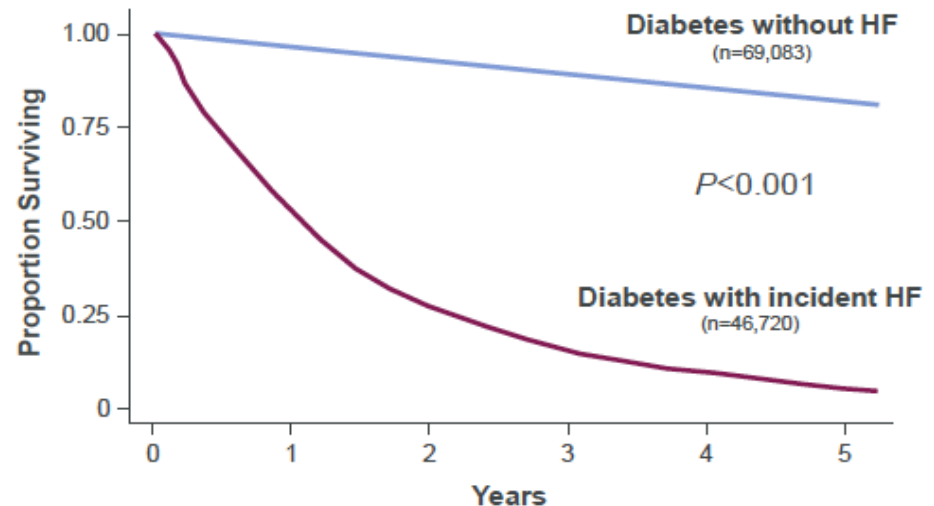
**HR for HF – 1.45 (1.34-1.57)**

Risk of Complications in Patients With Diabetes Relative to Patients Without Diabetes



Adapted from Bergenstal RM et al. *Am J Med.* 2010;123(4):374.e9-e18.

1. Foley RN et al. *J Am Soc Nephrol.* 2005;16:489-495. 2. Haffner SM et al. *N Engl J Med.* 1998;339:229-234. 3. Noel RA et al. *Diabetes Care.* 2009;32:834-838. 4. Trautner C et al. *Diabetes Care.* 1997;20:1147-1153.



# Treatment - T2DM

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- Differentiation between ‘micro’ and ‘macro’ vascular disease has limited clinical utility
- ‘Primary’ and ‘secondary’ prevention cohort for one disease may or may not have relevance to another disease
- For patients similar to those studied in the trials – SGLT2i should be used for incident HF risk reduction, irrespective of their effect on MACE outcomes
- For patients not studied adequately e.g. T2DM with no clear risk factors or with manifest HF – further data are needed

Pre-2015
HgbA1c
CV risk factors

2015-2018
HgbA1c
CV risk factors
Reduce CV Mortality
Reduce MACE risk

2018 onwards
HgbA1c
CV risk factors
Reduce CV Mortality
Reduce MACE risk
Reduce HF risk
Reduce CKD risk